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Review

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Polycystic ovarian syndrome review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age. It is characterized by a combination of hormonal imbalances, ovarian dysfunction, and metabolic disturbances. PCOS has significant implications for women's health, fertility, and overall well-being. This comprehensive review aims to provide an overview of PCOS, including its etiology, clinical manifestations, diagnosis, and management strategies.

Keywords: Infertility, insulin resistance, polycystic ovarian syndrome, PCOS,

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disease of reproductive-aged women with a lot of metabolic, reproductive, and psychological consequences. The pathophysiology of PCOS is complex, primarily caused by genetic mutations, hyperandrogenism, insulin resistance, persistent low-grade inflammation, and adipose tissue dysfunction. 2003 Rotterdam diagnostic classification is recommended, which requires two of the three: oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology[1]. Treatment options include lifestyle changes, pharmacological management such as combined oral contraceptives, metformin, antiandrogens, and combinations of them.

EPIDEMIOLOGY

PCOS is a common endocrine disorder in women of childbearing potential, with an estimated global prevalence of 5-15% using the Rotterdam Consensus Criteria.[1]

Depending on the diagnostic criteria being utilized, the prevalence ranges from 4-8% according to NIH/NICHD criteria to over 18% according to Rotterdam criteria.[2]

Besides the differences between diagnostic parameters, the level of occurrence varies by geographic (countryside vs. city) and personal factors (physical activity level, diet, etc.).[3] Some ethnic communities have been reported to have higher PCOS prevalence.[4] Han Chinese and Australian aboriginal populations are a couple of groups where PCOS has been researched.[4] There are racial and ethnic disparities in the prevalence of PCOS-related metabolic syndrome, which suggests the significance of dietary, climatic, or other lifestyle factors in the emergence of PCOS.[4] PCOS prevalence is higher among the races where obesity and insulin resistance are more common.[4]

Cosmetics that appear harmless, such as skin-whitening products, wrinkle creams, deodorants, sunscreen, and hair color, can disturb the hormonal balance, causing or exacerbating PCOS.[4]

PATHOPHYSIOLOGY

The pathophysiology of PCOS is complex and includes a wide range of abnormalities, mainly in the hypothalamic-pituitary-ovarian axis and insulin function. It involves a vicious cycle between hyperandrogenism, insulin resistance, persistent low-grade inflammation, and adipose tissue dysfunction (Table 1).

Also, genetic susceptibility and a strong correlation between several genes and pathways have been shown in PCOS pathophysiology. Genetic mutations, such as deletions, inversions, additions, and single nucleotide polymorphisms (SNPs) are potential contributors(Table 2).

Hyperandrogenism

Excessive levels of testosterone, androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone

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sulfate (DHEAS) are one of the main causes of PCOS development.

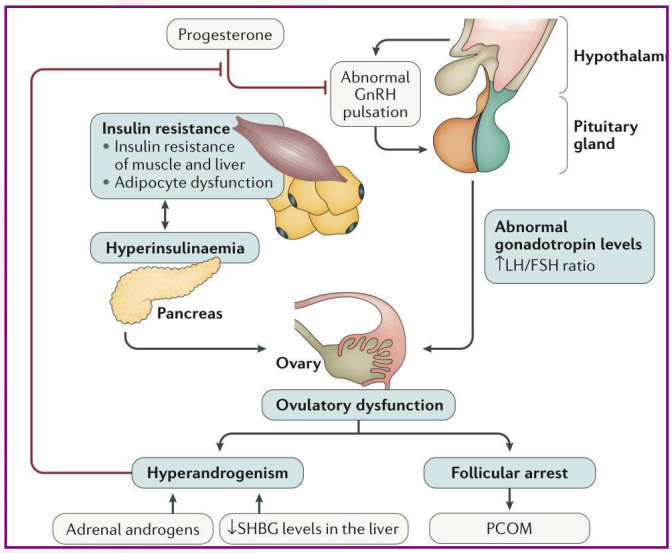

Table 1. Pathophysiology of PCOS[5]

FSH: Follicle stimulating Hormone, **GnRH:** Gonadotropin-releasing hormone, **LH:** Luteinizing Hormone, **PCOM:** Polycystic ovarian morphology

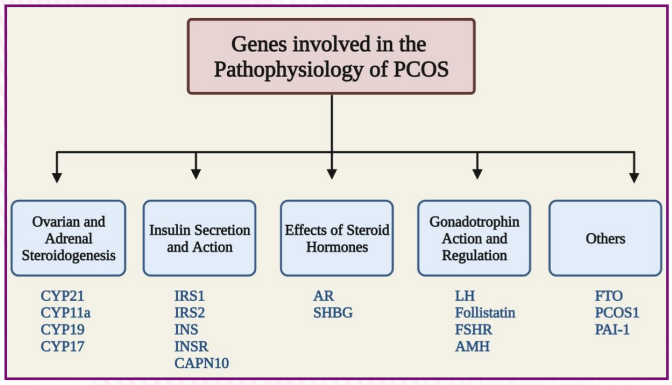

Table 2. Genes involved in the pathophysiology of PCOS[5]

CYP: cytochrome family p450; **IRS:** insulin receptor substrate; **INS:** insulin gene; **INSR:** insulin receptor; AR: androgen receptor gene; **SHBG:** sex hormone binding globulin; **FSHR:** follicle-stimulating hormone receptor; **LH:** lutein hormone e; **AMH:** anti-Mullerian hormone; **FTO:** fat mass obesity; **PAI-1:** plasminogen activator inhibitor 1; and **CAPN10:** caplain-10.

It is revealed that increased expression of several genes encoding steroidogenic enzymes causes exaggerated androgen synthesis in follicular theca cells.[6] Greater conversion of progestogen precursors to androgens caused by increased expression of CYP17A1 (the gene encoding the rate-limiting enzyme in androgen production) can be another contributor to the mechanism.[6]

An endocrine derangement in PCOS is the acceleration of GnRH pulsatile activity, which raises the frequency and pulse amplitude of LH over FSH, resulting in an increased LH/FSH ratio.[7] Interaction between high levels of LH and LH receptors promotes the proliferation of theca cells and furthermore contributes to the hyperandrogenic state.[8]

Despite the fact that the ovaries are the primary source of hyperandrogenism in PCOS, 20% to 30% of patients also have disproportionate adrenal androgen, caused by excessive ACTH secretion due to an imbalance in cortisol steroidogenesis.[9]

Insulin Resistance

Due to post-insulin receptor abnormalities, such as reduced glucose oxidation, impaired glucose phosphorylation, glucose synthesis and transport, insulin resistance is seen in PCOS patients.[10]

Insulin signaling is impaired in muscle due to increased serine phosphorylation of the insulin receptor and insulin receptor substrate 1 (IRS1).[11]

It is also shown that PCOS is linked to reduced GLUT4 (glucose transporter-4) expression as well as increased levels of oxidative stress in visceral adipose tissue, which had a direct correlation with insulin resistance.[12]

Hyperinsulinemia, caused by insulin resistance, increases androgen secretion from ovaries and adrenal glands, therewithal inhibits SHBG synthesis. Hence, the level of androgens increases. As can be seen, the production of insulin is greatly enhanced by androgen, but then androgen is further stimulated by insulin, creating an endless loop. In this regard, insulin resistance and metabolic problems are more prevalent in hyperandrogenic PCOS phenotypes.[13]

Chronic Inflammation

In many studies, it is revealed that chronic inflammation state contributes to the pathophysiology of PCOS. Inflammatory cytokines, especially tumor necrosis factor alpha (TNF-α) and interleukin beta (IL-β), play an important role.[14] Increased leukocyte count, C-reactive protein (CRP), IL-6, IL-18, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1 can also be seen.[15]

Recent studies showed that increased levels of advanced glycosylation end products (AGEs) and their receptors are other contributors to inflammation in PCOS.[16]

Adipose Tissue Dysfunction

Adipocytes and adipocyte activity are dysregulated in PCOS, favoring insulin resistance and subclinical inflammation even though women with PCOS may exhibit different distributions of fat or total BMI. It is demonstrated that women with PCOS appear to have larger adipocytes and decreased lipoprotein lipase activity.[17,18]

CLINICAL FEATURES

SYMPTOMS

PCOS affects both adolescents and adult women, which is a condition with a variety of distinct manifestations.[19] Patients apply to the clinics with various symptoms that affect their physical appearance and quality of daily life.

Immune and metabolic abnormalities are encountered due to chronic low-grade inflammatory state in PCOS.[20] Since recent years, the pathogenic function of immunological dysregulation in PCOS has been implicated in the alteration of several organ systems throughout the body, besides the female reproductive system.[20] This includes gynecological

symptoms such as oligomenorrhea, amenorrhea, and infertility as well as dermatological symptoms including hirsutism, acne, and alopecia.[19]

Oligomenorrhea / Amenorrhea

In the first one to two years following menarche, irregular menstruation is frequent.[21] The majority of girls experience normal monthly cycles by their fifth gynecological year as cycle variability gradually reduces over time.[21] To be identified as oligomenorrheic, an adolescent girl must have less than four menstruation periods in a year if she is in the first postmenarchal year, and fewer than eight menstruation periods if she is postmenarchal by 3-5 years.[21] Five years after menarche, criteria for adults (less than nine periods annually) are used.[21] It's significant to note that menstruation intervals longer than 90 days are unusual, even in the first year following menarche.[21]

If the cycle is disturbed, amenorrhea may develop. This condition can be either primary or secondary.[21] Secondary amenorrhea, also known as hypothalamic amenorrhea, is defined by the lack of menstrual periods for three or more consecutive months, whereas primary amenorrhea is the failure to achieve menarche due to chromosomal or structural abnormalities.[21]

Infertility

PCOS is the primary cause of infertility as a concern of public health, impacting 8–13% of women of reproductive age.[22] It has been suggested that ovarian disruption, a key mechanism in anovulation and infertility, is caused by androgen excess, insulin resistance, and hypothalamic-pituitary dysfunction.[22]

The development of primordial follicles, selection of a dominant follicle, and ovulation are all normal steps in the ovary's life cycle.[21] The disruption of this recurrence pattern in PCOS emerges.[21] Even if several follicles develop, none of them become dominant.[21] Ovarian ultrasound imaging can show the polycystic ovaries as atresia of the follicles become evident.[21]

Patients with PCOS frequently have more than 12 cysts that are 8 mm in size in the ovary.[23] This condition makes around 70% of females infertile.[24]

In order to manage reproductive functions in PCOS patients, lifestyle changes may be counted as the first non-pharmacological treatment option When all non-pharmacological options fail, ovulation induction can be provided with pharmaceutical agents such as letrozole, clomiphene citrate (CC), metformin, and gonadotropins. Women with PCOS and anovulatory infertility are typically treated with letrozole as their first option.

Hirsutism, Acne and Alopecia

Hyperandrogenism has clinical manifestations such as hirsutism, acne, and androgenic alopecia. It is stated that hirsutism is seen in 65-75% of PCOS patients.[24] Although it is uncertain if the prevalence of acne is much higher in these individuals than that seen in the general population, 15–25% of PCOS patients experience acne, and ethnicity has an impact on this prevalence.[24] In order to restore the menstrual cycle and cure acne and hirsutism in women with PCOS, hormonal contraception is frequently used, sometimes in combination with antiandrogens.[25]

COMPLICATIONS/OUTCOMES

Infertility, obstetrical problems, endometrial cancer, mental disorders, metabolic abnormalities such as obstructive sleep apnea, dyslipidemia, obesity, and type 2 diabetes mellitus (T2DM) are all more common in women with PCOS. These women also have a higher risk of ovarian cancer, venous thromboembolism, cardiovascular and cerebrovascular events, and stroke.[18]

Metabolic Abnormalities and T2DM

A bidirectional association exist between PCOS and excess adiposity, with PCOS itself appearing to predispose to weight gain while excess weight aggravates the underlying hormonal imbalance.[26] Up to 37% of women who are overweight have PCOS.[27] A longitudinal analysis using the Northern Finland Birth Cohort 1966 Study also found a link between PCOS and increased body mass index (BMI) around the age of 6 caused by early adiposity.[28]

Adipose dysfunction caused by invasion of macrophages, inflammatory state, and insulin resistance is linked to obesity [21]. In this regard, obesity increases the risks of cardiometabolic disease by aggravating hyperinsulinemia. But also it is shown that a large portion of PCOS-affected women exhibit basal and glucose-stimulated hyperinsulinemia as well as insulin resistance regardless of BMI.[18] Insulin resistance not only plays a significant role in the pathogenesis of PCOS but also severely impacts PCOS patients by increasing their risk of chronic illnesses including T2DM and cardiovascular disorders.[5]

Endometrial Hyperplasia

Persistent anovulation, unopposed action of estrogen, and the absence of inhibitory effects of progesterone cause endometrial hyperplasia, which is another complication of PCOS.[29] Prolonged exposure to unopposed estrogen along with little or no endometrial shedding can induce endometrial hyperplasia, which can eventually turn into endometrial cancer.[29]

Gestational Diabetes Mellitus (GDM)

Beyond its impact on fertility and menstrual irregularities, PCOS has been associated with various perinatal outcomes. Women with PCOS have an increased risk of developing gestational diabetes mellitus during pregnancy.[30] The hormonal and metabolic abnormalities associated with PCOS, such as insulin resistance and impaired glucose tolerance, contribute to the development of GDM.

Psychological Distress

PCOS-diagnosed patients are more likely to experience severe

psychological distress, decreased well-being, despair, and worries about their future health and ability to conceive.[31] Patients also experience anxiety, depression, changes in eating habits, sexual dysfunction, and dysmorphic disorders after diagnosis.

Programs for mindfulness meditation have grown in popularity over the past several decades and are now being used in clinical studies to lower stress and enhance psychological wellness in patients with a variety of medical illnesses.[31] The synthesis of adrenal androgens, which are generated by the adrenal glands as a direct response to psychological discomfort, can be decreased by mindfulness meditation.[31]

DIAGNOSIS

DIAGNOSTIC CRITERIA

After Stein and Leventhal described PCOS for the first time in 1935 in a case series of seven women with hirsutism, obesity, amenorrhea, and bilateral enlarged polycystic ovaries, different diagnostic criteria have been made.[32]

NIH Criteria

The first attempt to develop standard diagnostic criteria for PCOS was at the National Institutes of Health (NIH) international conference in the early 1990s.[33] PCOS diagnosis is made if patients have all of the following criteria after excluding all other conditions linked to hyperandrogenism or anovulatory infertility:

- Oligo-anovulation,
- Clinical and/or biochemical signs of hyperandrogenism.

Using the NIH definition, the prevalence of PCOS has remained stable at 5-8%.[34]

Rotterdam Criteria

In 2003, experts gathered in Rotterdam (Netherlands) at a meeting sponsored by the European Society of Human Reproduction (ESHRE) and the American Society for Reproductive Medicine (ASRM) and agreed on new criteria.[2] PCOS diagnosis is made if patients have two of the following:

- Oligo-anovulation,
- Clinical and/or biochemical signs of hyperandrogenism,
- Polycystic ovarian morphology (PCOM) on ultrasonography.

As a result, several studies found that the prevalence of PCOS was up to three times higher than when the 1990 NIH criteria were used for diagnosis.[35]

According to the Rotterdam criteria, PCOS cases are divided into four phenotypes (depending on whether the three diagnostic criteria are present or not) as seen in the **Table3.**

Table 3. Phenotypes of PCOS

	Oligo-anovulation	Hyperandrogenism	PCOM
Phenotype A	+	+	+
Phenotype B	+	+	
Phenotype C		+	+
Phenotype D	+		+

PCOM:Polycystic ovarian morphology

AES Criteria

In 2006, the Androgen Excess Society (now known as the Androgen Excess-PCOS Society) asserted, that a PCOS diagnosis should be made if patients have all of the following criteria [36]:

- Clinical and/or biochemical signs of hyperandrogenism,
- Ovarian dysfunction, including oligo-anovulation and/or PCOM,
- Exclusion of other androgen excess-related disorders.

As a result, phenotype D based on the Rotterdam criteria was no longer considered PCOS.

These several diagnostic criteria have contributed to clinical uncertainty, hence the NIH held an evidence-based methodology workshop on PCOS in 2012, and it is advised to use the broader Rotterdam criteria with phenotypic specification.[35] Despite being the most widely used classification, using the Rotterdam criteria has not yet gained worldwide acceptance.

CLINICAL DIAGNOSTIC APPROACH

Menstrual periods that last more than 35 days or fewer than 21 days defined as amenorrhea requires further investigation in patients.

Hirsutism, alopecia, and acne are clinical symptoms of hyperandrogenism. Given that, only 60% of PCOS patients exhibit symptoms of hyperandrogenism, the diagnostic criteria for hyperandrogenism were expanded to include biochemical signs.[36] Regarding the ideal biochemical test for androgen excess, there is not a full consensus. The amount of SHBG has no impact on the assessment of free T, in contrast to total T. Measuring free T, total T, or calculating the androgen index is suggested.[37] It is strongly advised against doing tests for AMH, FSH, or insulin levels.[37]

To be able to say polycystic ovarian morphology, at least 25 small follicles (2 to 9 mm) must be found in the ovary.

PCOS can be difficult to diagnose in adolescents. Since anovulatory menstrual periods in the first several years postmenarche and also large polycystic ovaries can be seen, using classical diagnostic criteria is not reliable.[38]

TREATMENT

The patient's characteristics will determine the management strategy and optimum therapeutic option in PCOS patients. Infertility treatment, menstrual cycle control, weight loss, or alleviation from hyperandrogenic symptoms such acne, hirsutism, or androgenic alopecia may be counted as the symptomatic relieve in PCOS management. Pharmacological treatments and surgical procedures are both available for PCOS.

Lifestyle Modifications

The initial therapy suggestion emphasizes proper nutrition and physical activity regimens, especially for PCOS patients who are overweight or obese.[21]

Even modest weight loss with changing eating habits in obese women with PCOS improves biochemical reproductive outcomes, insulin resistance indicators, adiposity, and its distribution.[39] 2013 clinical practice guidelines from the Endocrine Society recommend using exercise therapies to treat obesity and overweight in PCOS patients.[4]

Combined Oral Contraceptives

The functional cysts associated with PCOS might go away on their own. However, certain cysts have the potential to burst and bleed, which can cause sudden, intense discomfort in the lower abdomen.[4] The combined oral contraceptives (COCPs), when used for six months, reduce hyperandrogenism and regulate menstrual cycles by inhibiting ovulation and cyst formation.[39]

COCPs also reduce androgens, raise SHBG levels, prevent conception, and maintain the integrity of the endometrial structure.[39] The available data indicate that there are no appreciable changes in body weight or glucose tolerance associated with COCP use in adult women, although there are increases in total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations.[39]

Although it is important to take risk factors into account such as hypertension, obesity, clotting history, and smoking, there is no evidence to show that women with PCOS who use oral contraceptives have more cardiovascular events than women in the general population.[39]

Metformin

Metformin is an insulin sensitizer that is frequently used to treat insulin resistance in PCOS patients. When it comes to reducing body weight, metformin is comparable to lifestyle changes, but it works better when it comes to lowering androgen levels. In comparison to lifestyle adjustments alone, the combination of metformin plus lifestyle changes provides increased quality of menstrual periods, reduced BMI, subcutaneous adipose tissue, and glucose levels in PCOS patients. It also has a mild to moderate impact on lowering cholesterol levels and relief of insulin resistance.[40]

Clomiphene citrate (CC) alone or in combination with metformin is advised for treating infertility in PCOS. There is proof that metformin has an advantage over placebo and CC alone in terms of pregnancy and ovulation rates. Therefore, rather than continuing with CC alone, especially in PCOS patients who are CC-resistant, CC might be coupled with metformin.[41,42] However this is also accompanied by a rise in multiple pregnancies (5-8%) and ovarian hyperstimulation syndrome (1%).[42]

Antiandrogens

Spironolactone, flutamide, and finasteride are antiandrogens that slow the development of new terminal hairs, which can be used to treat symptomatic complications of hyperandrogenism due to PCOS. Antiandrogens prevent the development of the external genitalia of male fetus, necessitating the use of very effective birth control at the same time. A very uncommon adverse effect of spironolactone is hyperkalemia.[21]

ETHICAL DECLARATIONS

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